TOBACCO INDUSTRY RESEARCH COMMITTEE

CONFIDENTIAL

TIRC Grants #33, -R1, 160, 213

Dr. Marion B. Sulzberger (Redisch)
New York University-Bellevue Medical Center

Progress Report #2
February, 1959

"Investigation of the Effects of Tobacco on the Human Vascular System in Healthy Volunteers as well as in Patients with Occlusive Vascular Disease; Particular Attention to be Directed at the Possibility that Certain Tobacco Effects are Based on Peculiar Allergic Susceptibility of Specific Individuals Rather than Upon Obligatorily Toxic Products in Tobacco Smoke. Also, the Possible Influence of Habitual Smoking Upon Vascular Responses is to be Ascertained."

## Introduction

There has been considerable interest in vasomotor responses to nicotine and to the smoking (or chewing) of tobacco for many years. There is almost complete agreement that smoking usually produces transient adrenergic stimulation via the sympathetic nervous system followed by depression of sympathetic and parasympathetic ganglia. Vasoconstrictive effect to tobacco smoking could not be elicited in sympathectomized limbs by the technique of toe plethysmography, which records skin flow only.

It has been fairly well established over the years that in a certain percentage of subjects, smoking of tobacco causes vasoconstriction of peripheral vessels as indicated by decrease in surface temperature and also by plethysmographically measured blood flow. The mechanism involved in this response has been the subject of some controversy. Mulinos and Shulman found that deep breathing per se may cause reflex vasoconstriction (and, consequently, diminution of peripheral blood flow measured plethysmographically) in fingers, hand and forearm. Bolton et al found similar changes. In contrast, Evans and Stewart believe that vasoconstrictor effect of smoking is neither due to nicotine nor to deep inhalation but rather to "irritation" by smoke per se. These authors based their opinion on the observation that smoke not containing any nicotine produced the same effect on peripheral circulation as did tobacco smoke, and that drawing on an unlighted cigarette produced no vasomotor effect. Others support the notion that nicotine is the effective agent and that smoking is merely a way of administering nicotine. Roth et al found that changes in peripheral vascular circulation produced by denicotinized and corn silk cigarettes were negligible.

Likewise, discrepant views concerning the vascular beds involved in constrictor responses to tobacco smoking have been expressed in the literature. Friedlander and associates found that following tobacco smoking the greatest decrease in blood flow occurred in the skin. This opinion is shared by other investigators. Abramson and co-workers believe that vasoconstriction following tobacco smoking is limited to the skin and that muscle flow is not affected at all. On the other hand, Fletcher found plethysmographic evidence of blood flow diminution of as much as 40%, without changes in surface temperature using an air transmission finger plethysmograph. He believes that skin temperature is not a reliable index of peripheral vascular response.

1003541301

Source: https://www.industrydocuments.ucsf.edu/docs/yfvm0000

Allergic-hyperergic mechanisms are also thought to be involved in the bodily response to nicotine, and the skin reaction to tobacco is believed by some to be a specific allergic response rather than an "irritative" reaction. Sulzberger showed that of 400 normal smokers, 32% reacted with a positive skin test to tobacco extracts and to extracts of timothy or horse dander; of these 32%, 9% reacted to tobacco only. Green reported that 13 of 100 normal smokers reacted positively to tobacco extracts. Romanoff and Rubin found 16 positive skin reactions to tobacco among 68 normal smokers. Trasoff reported 17% positive skin reactors in 40 normal smokers. The number of positive skin reactions to tobacco is obviously dependent upon the type of subjects used. It increases considerably when one is dealing with patients with thromboangitis obliterans. Cooke reported 78% positive skin reactions to 5 tobacco extracts and extracts of ragweed, timothy and horse dander in 140 patients with Buerger's Disease, compared with 9% positive skin reactions to tobacco in 400 unselected normal smokers. Forty-four of 95 patients with thromboangitis obliterans also demonstrated antibodies to tobacco on passive transfer. Sulzberger, Romanoff and Rubin reported similar findings.

Because of these observations it seemed of interest to correlate responses with sensitivity responses in the skin. During the study it became clear that in order to arrive at a definitive conclusion, different age groups, smokers and non-smokers, would have to be included and that comparison of patients with vascular disease with "healthy" subjects was necessary.

This first report deals merely with the findings in a group of 80 healthy smokers, none more than 50 years of age.

## Methods and Material

Measurements of peripheral blood flow, recordings of surface temperature, heart rate and blood pressure were done in all subjects before and after smoking. Eighty healthy subjects were tested (27 females and 53 males), their ages ranging from 18 to 50 years with a mean of 36. Blood flow to the leg and foot was measured by means of a large limb venous occlusion plethysmograph, using an air transmission system connected to a strain gauge which permitted expression of very small pressure changes in terms of volume changes. Sudden venous occlusion was accomplished by a stopcock system, connected to a large pressure reservoir. Surface temperature was recorded continuously on a six-channel Leeds and Northrup Speedomax. All tests were performed in the Constant Temperature Room at 28°C and 55% humidity. Subjects were considered "adapted to the environment" when the toe temperature had remained constant for at least a $\frac{1}{2}$ hour. All subjects were obliged to refrain from smoking and eating at least one hour before the test. Three plethysmographic base line tracings were obtained at five minute intervals after adaptation, then one test cigarette (containing a well equilibrated mixture of Burley, Virginia and Turkish tobaccos and mixed fatted and defatted tobacco) was smoked in six minutes. The amount of smoking of the single cigarette used here as stimulus was considered sufficient since it has been shown that one cigarette produced as much change as can be elicited in a given individual; a second cigarette does not alter the response. Subjects were encouraged to smoke in their accustomed manner. Three to four minutes after smoking was finished, another three tracings at five minute intervals were taken. Since electrocardiography and ballistocardiography have been widely used in assessing the effects of smoking on the coronary circulation, it was decided to

1003541302

Source: https://www.industrydocuments.ucsf.edu/docs/yfvm0000

add these methods to the measurement of peripheral blood flow. Electrocardiograms were taken, including standard leads, unipolar leads and V1, V3, V5; and ballistocardiography was performed simultaneously (D-V-A ballistocardiograph model A2-Arbeit)*. Blood pressure and pulse rate were recorded before and after smoking. The following arbitrary criteria for significance of changes were accepted on the basis of previous experience:

1. Change of blood flow of at least 2 ml per minute per 100 ml tissue.
2. Change in surface temperature of at least 2°C.
3. Depressions of S_T and flattening of T waves (< 2 mm) in the electrocardiogram.
4. Ballistocardiographic tracings were interpreted empirically, in a qualitative way on the basis of the following criteria:
   - Grade 0: Normal tracing; all IJK complexes normal in configuration and identical.
   - Grade I: Normal tracing: minor variations in IJK complexes which are still normal.
   - Grade II: Probably abnormal; significant variation in individual complexes, especially in the IJ wave.
   - Grade III: Abnormal; marked abnormalities in the individual complexes, some of which are still identifiable.
   - Grade IV: Markedly abnormal; the tracing is chaotic and there are no IJK complexes identifiable, as such.
5. Changes of arterial pressure of at least 20/20 mm Hg.
6. Change in heart rate of at least 15 beats/min.

The 80 subjects reported were also tested with intradermal injections of the (various) tobacco extracts (Burley, Virginia, Turkish, mixed fatted and defatted tobaccos) on the lateral aspects of the arm and reactions read after 10 minutes.** The preparation of the tobacco extract was made according to the procedures which have been chosen by the Allergy Laboratory of the University Hospital of N.Y.U. from raw, untreated, sun-dried tobacco. Immediate wheal type reactions exceeding 10 millimeters were considered to be positive, and reactions subdivided into moderate and marked positive reactions (slightly positive reactions were not taken into consideration). Correlation of changes in blood flow with skin sensitivity was made subsequent to the independent observation.

1003541303

Results

Of the total 80 healthy subjects, 38 (47.5%) revealed changes in at least one of the above circulatory measurements after tobacco smoking, while 42 subjects (52.5%) showed no response. Only 10 subjects showed changes in the ballistocardiogram and only 3 in the EKG. We do not feel that any conclusions would be warranted from these figures.

---

* - We wish to express our sincere thanks to Dr. Sidney Arbeit for supplying us with his D-V-A ballistocardiograph for this work and aiding us with his great experience in the interpretation of the ballistocardiograms.

** - This part of the work was done by Drs. Sulzberger, Fontana and associates, who reported their results in detail at the 14th Annual Meeting of the American Academy of Allergy in Philadelphia, Pa., February 3, 1958.

Source: https://www.industrydocuments.ucsf.edu/docs/yfvm0000

subjects
Twenty-eight/(35%) showed a significant decrease in the plethysmographically measured blood flow. Fifty-two (65%) showed no change, none showed an increase. We therefore concentrated on the evaluation of changes in plethysmographically measured extremity blood flow, in this first group of subjects.

Of the 80 subjects, 32 (40%) showed a positive skin reaction to the tobacco extracts, described above, and 48 (60%) remained negative. Of the 48 subjects with negative skin test to tobacco, 43 revealed no significant change in measured peripheral blood flow after smoking; the remaining 5 subjects showed a significant decrease in blood flow. On the other hand, of the 32 subjects with positive skin test to tobacco, 21 (65.6%) showed a decrease in blood flow after smoking, while 11 showed no change.

## Discussion

Correlation between skin testing for tobacco extract and blood flow changes after smoking the mixture appears significant as far as negative responses were concerned. It seems from our figures that in a group of "healthy" smokers, simple skin testing might be a fairly reliable way of screening out those subjects in whom smoking will, in all probability, not cause any decrease in peripheral blood flow. This may be expected to comprise about 90% of all negative "skin reactors" in a given group or a total of about 60% of all "healthy" smokers. To screen the remaining 40% for positive blood flow responses would require plethysmographic measurements. The latter procedure is so much more cumbersome and time-consuming than skin testing that it would be of notable practical advantage to first use skin testing if and when screening is desired. The same type of correlative testing is now being applied to healthy non-smokers and to smokers and non-smokers with occlusive arterial diseases and will be reported upon completion.

There remains the fact, that responses in surface temperature and in plethysmographically measured blood flow of the lower extremity did not correlate in this group of 80 healthy subjects. The significance of this has to be ascertained through further work. The clue might well be that blood flow to the leg indicates predominately muscle flow, while surface temperature is a function of skin flow only.

## Summary

Of a group of 80 healthy smokers, 32% showed a decrease in plethysmographically measured extremity flow in response to smoking. Comparison with skin testing revealed a significant correlation in negative responses only; 90% of those who did not react to skin testing with tobacco extract had no decrease in peripheral blood flow in response to smoking.

1003541304



Source: https://www.industrydocuments.ucsf.edu/docs/yfvm0000